Remarks

Claims 1, 3 – 13, and 15 – 17 are pending.

The amendment to claim 1 is based on specification page 11, lines 14 – 16.

The Office Action mailed December 19, 2006 states that the Information Disclosure Statement filed July 19, 2004 was not accompanied with copies of the foreign patents and non-patent literature. Applicants telephoned the Examiner to notify him that the subject foreign patents and non-patent literature were made of record in the parent application serial number 09/909,560 on February 4, 2002 and February 19, 2003. See 37 CFR 1.98(d). Applicants request that the examiner consider these references and make them of record.

The examiner has requested that the trademarks Chiralpak and Zorbax be capitalized and used with generic terminology. The requirement for capitalization is not understood as applicants believe these terms are in fact capitalized wherever used. As for generic terminology the Chiralpak product is defined on specification page 30, lines 14 – 18 (Chiralpak is a chiral column packing material) and used generically there. While Chiralpak is used on page 31, in view of the statements on the previous page in relation to this product, the page 31 useage is not believe to constituted trademark misuse. The specification has been amended to recite the generic function of the Zorbax product.

Applicants gratefully acknowledge the withdrawal of the objection to claims 4, 5 and 12, the rejection of claim 7, and the rejection of claims 1, 3-5, 9 and 14 – 16 under 35 USC 102(b) over Glazier et al.

Claims 1 and 3 -7 were newly rejected under 35 USC 102(b) as being anticipated by Shaw et al. Applicants respectfully disagree with the examiner that the citation of this reference was necessitated by the last amendments; Shaw et al. was as applicable to the original claims as it is

to the amended ones, to the extent the rejection is meritorious. Applicants request that the finality of the rejection be withdrawn and a new period for response be set.

According to the examiner, Shaw teaches a screening method comprising providing a prodrug of PMPA, selecting plasma as a target tissue and intestine and liver as non-target tissue, administering prodrug to both tissues and determining the relative *in vitro* biological stability and bioavailability of the PMPA in the tissues. This rejection is respectfully traversed.

The examiner's attention is respectfully drawn to specification page 11, lines 8 – 16. Here applicants point out that the method of this invention is distinct from studies undertaken to determine oral bioavailability of prodrugs. Shaw et al. is such a study. In Shaw et al. one simply looks at the stability against hydrolysis of the prodrugs, and at oral bioavailability. Shaw et al. did not have as their objective the determination of differential antiviral or antitumor activity in the tissues being sampled; they were simply looking at the stability of the prodrugs to hydrolysis (or their ability to pass through the gut into the circulation).

As applied to claim 1, Shaw et al. fails to meet the target tissue limitation. Plasma is not a tissue. It is the liquid fraction of blood from which cells have been removed. Applicants define tissue as including at least cells from a defined source (specification page 11, line 29). It should be pointed out as well that applicants consider small intestine to not be a target tissue (specification page 11, lines 14 – 16), in keeping with their intent to exclude bioavailability studies from the scope of their claims.

Shaw et al. were testing both intestinal homogenate and liver homogenate in their method. The possibility that these homogenates could be construed to be a target/non-target tissue is excluded by the amendment to claim 1.

The Shaw et al. administration of the prodrugs to live dogs also does not anticipate the claims. Shaw et al. were simply determining the ability of the prodrug to produce active drug in the circulation after oral administration. Shaw et al. do not disclose administering the prodrug and then assaying its conversion to parental drug <u>in target vis a vis non-target tissues.</u> Applicants'

method contemplates determining *differential* activity in various tissues. In the case of the live dog, this was not done.

The examiner is respectfully requested to reconsider and withdraw the rejection under 35 USC 102(b).

Claims 1, 3-7 and 10-13 were rejected under 35 USC 103(a) as being unpatentable over Shaw et al. Applicant reiterates its remarks regarding the prematurity of this rejection, and respectfully asks for the same remedy.

The examiner acknowledges that Shaw et al. do not administer the prodrug to an animal and then determine the activity of the drug in individual tissues after administration. The examiner takes the view that this would have been obvious in order to evaluate the effect of "other variables" such as "enzymes, hormones, etc." This rejection is applicable only to claim 10, which is the sole claim reciting testing in a live animal. In any case, the rejection is respectfully traversed.

Fundamentally, nothing but hindsight motivates this rejection. It is far less trouble to measure prodrug stability in tissue homogenates than in an intact animal, and the examiner has not provided any credible evidence for the assertion that "other variables" would direct the change. The enzymes, hormones and the like would be in the homogenates just as they are in whole animals. Shaw et al. use intact animals, but only for the conventional oral bioavailability study. The fact that they did not use intact animals instead of homogenates when looking at individual tissues is instructive that the use of intact animals would not have been obvious for the individual tissues. Further, in any case, it would not have been obvious to omit the intestinal assay from Shaw et al. because this was critical in determining oral bioavailability.

The Office is respectfully requested to reconsider and withdraw the rejection under 35 USC 103 over Shaw et al.

Claims 1, 3 -7, 9 – 13, 15 and 16 were rejected under 35 USC 103(a) as unpatentable over Shaw et al. in view of Glazier et al. The examiner takes the view that it would have been obvious to

"combine" the screening methods of these references because both are "the determination of the relative antiviral activities of phosphonoamidate prodrugs in various tissue types". This rejection is respectfully traversed.

Glazier et al. was deficient because it does not teach determining antiviral activity in *different* tissues. Instead, Glazier et al. was comparing activity of the test compounds in paired infected and uninfected cells (from the same tissues).

Shaw et al., on the other hand, have an entirely different objective. They are not looking at antiviral activity, they are looking at prodrug stability in individual tissues. Their objective is to measure the convertibility of the prodrug to parental drug in intestinal and liver homogenates. They are not concerned with whether the parental drug has any antiviral activity IN the various tissues – they already knew that.

There is no basis for combining these references except hindsight, and even then the combination would not reach the claims. Even assuming the references could be logically combined, combining Glazier et al. with Shaw et al. would have Shaw et al. testing stability in infected homogenates and uninfected homogenates. In addition, there would be no reason to drop the intestinal homogenate (amended claim 1) since it is central to the Shaw et al. inquiry.

The examiner is respectfully requested to reconsider and withdraw this rejection.

Claims 1, 3 – 8, 10 – 13 and 17 were newly rejected under 35 USC 103(a) as being unpatentable over Shaw et al. in view of Starrett et al. This rejection appears to apply to only to claim 8 (which calls for an aryl ester prodrug) and claim 17 (where the tissue is hematological and the activity is antitumor activity). This rejection is respectfully traversed.

According to the examiner, Starrett et al. teaches administering a PMEA prodrug to rats and assaying the appearance of the parental drug in urine. PMEA is reported by Starrett et al. to have anti-tumor activity. Shaw is determining bioavailability and tissue stability of a prodrug. The examiner suggests that it would have been obvious to combine the two references because both

are concerned with "bioavailability of prodrugs in animals." This rejection is respectfully traversed.

Starrett et al. is simply duplicative to the bioavailability study of Shaw et al. The only difference is that Starrett et al. measured bioavailability by looking for the metabolite in the urine; Shaw et al. looked for it in the plasma. There is no reason to combine the methods – at best, they are alternatives. Coming from the other direction, Shaw et al. could have tested the PMEA prodrug in their method of determining stability (using tissue homogenates), but the issue of tumors would have been irrelevant. In any case, Starrett et al. does not supply the deficiency of Shaw et al. with regards to the amended claim 1.

This application is now believed to be in condition for allowance. An early notice to that effect is solicited.

Respectfully submitted,

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